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New Vinca Alkaloids and Related Compounds

Daniel R. Budman

The vinca alkaloids remain among the most useful classes of anticancer agents used in the clinic today. However, previous analogs of these agents have not realized either increased safety or an enhanced antitumor spectrum. Currently, three derivatives are in clinical trial: vinorelbine, vintripol, and vinxaltine. Vinorelbine has shown consistant antitumor activity in patients with breast carcinoma and is in phase III trials in the United States, Europe, and Japan. Vintripol and vinxaltine, vinca alkaloids conjugated to amino acids, are in early clinical trials in Europe. The dose-limiting toxicity of these agents is leukopenia. A similar agent with a different chemical structure, rhizoxin, is in early phase II clinical trials with initial activity noted in breast carcinoma. The ultimate role of these agents in treatment of human malignancy awaits the results of ongoing studies.

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THE VINCA ALKALOIDS have become clinically useful since the discovery of their antitumor properties in 1959. Initially, extracts of the periwinkle plant (*Catharanthus roseus*) were investigated because of putative hypoglycemic properties but were noted to have the ability to cause marrow suppression in rats and antileukemic properties in murine tumor systems.[1] At that time, 30 alkaloids were isolated with 4 showing reproducible antitumor activity and 2 of them, vinblastine and vincristine, becoming commercially available.[1] These agents were noted to have a broad antitumor spectrum in humans with well defined, reversible toxicities leading to widespread use. As a result, analogs of these drugs have been developed over the past 30 years in attempts to decrease toxicity, increase the antitumor cytotoxicity, and broaden their action to more common types of tumors. However, only one additional vinca alkaloid has become commercially available in many countries, Vindesine, and this drug has not proven to be sufficiently different from the parent compounds to secure new drug status for commercial marketing in the United States.

The effort to discover congeners of the vinca alkaloids that are more effective or less toxic continues because of interest in the mechanism of action of these agents, the easy availability of the parent molecule as a source for chemical modification, the well known chemistry of these drugs, the robust methodology for analysis of these agents in fluids and tissues, and the good chemical stability of many of these drugs in solution. In addition, vinca alkaloids have been conjugated to monoclonal antibodies for biological therapy. However, drugs of this class have not received the same attention as the taxanes (taxol and taxotere), which are under accelerated development[2] and have a separate mode of action on tubulin.

PRECLINICAL PROPERTIES

The vinca alkaloids have been under active investigation in the laboratory for many years and their inhibition of microtubule formation in cells could be the subject of a separate article. The vinca alkaloid molecule is composed of two parts: a large multiple ring structure called catharanthine (the upper half of the vinca structure) and a lower multiple ring domain called vindoline. Recent information suggests that the catharanthine ring of the drug is responsible for the binding of the vinca alkaloid to tubulin with the vindoline ring enhancing the binding process and allowing the drug to interfere with normal microtubule formation.[3] Specific modifications of the catharanthine molecule, such as C-20′ alkyl analogs of vinblastine, have been used to analyze the interaction of this drug with tubulin. Small modifications of the side chains can result in large biological differences.[4] There are at least two binding sites for drugs on tubulin: a vinca binding site and a colchicine binding site. The ability of these drugs to inhibit tumor cell proliferation is dependent on their ability to (1) cause a metaphase arrest of cell division, (2) accumulate between 16- and 63-fold higher in cells than the surrounding fluids, (3) inhibit the normal microtubule extremities from functioning, and (4) occur at

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concentrations lower than those needed to prevent full microtubule assembly.[5] As inhibition of microtubule formation requires the hydrolysis of guanosine triphosphate (GTP), workers at the National Cancer Institute (NCI) have recently developed a tubulin-dependent GTP hydrolysis assay to screen for new vinca-like drugs.[6]

Uptake of vinca alkaloids into cells seems to involve two processes: (1) a rapid energy independent uptake and (2) a slower energy dependent process.[7] The latter mechanism may be more important when these agents are administered as a prolonged infusion. In addition, egress of this class of agents is in part under control of mechanisms such as the multiple drug resistance (MDR) pump.

Many agents inhibiting tubulin formation have progressed to the preclinical stage of drug development and may eventually undergo human trials. These drugs include such diverse structures as a polypeptide isolated from the sea hare (*Dolabella auriculata*), dolastatin 10, and combretastin A4 isolated from a South African tree (*Combretus caffrum*).[8] Dolastatin 10 noncompetitively binds to tubulin at a site believed to be different from the vinca or colchine binding site.[9] Combretastin A4 binds to the colchine binding site and is not affected by the MDR pump.[8] Synthetic compounds have also been found to inhibit microtubule formation and are currently under development. These agents include MDL 27048 (Merrill-Dow Corp.) (trans-1-2,5-dimethooxyphenyl)-3-(4-(dimethylamino)phenyl)-2-methyl-2-propen-1 -one), which rapidly and reversibly binds to the colchine binding site,[10] the derivatives of 1-deaza-7,8-dihydropteridines,[11] and imidazopyridazine carbamates (1069C) active in murine cell lines resistant to vincristine or doxorubicin.[12] New analogs of vinca alkaloids modified on the vindoline ring at C4 have shown enhanced activity compared with vincristine or vinblastine in murine xenografts and are under consideration for further development.[13]

NEW VINCA ALKALOIDS

Vinorelbine

Vinorelbine (Navelbine, 5′-noranhydrovinblastine, Burroughs Wellcome Co.) has already been the subject of an entire issue of *Seminars in Oncology* (Volume 16, Supplement 4, 1989), and currently is in phase II and phase III trials around the world. In tissue culture, cells can be made resistant to this semisynthetic vinca that are cross-resistant with other vincas but not anthracyclines, implying that mechanisms other than the MDR pump may exist.[14] In murine P 388 leukemia, resistance is associated with a MDR mechanism.[15] Vinorelbine has shown classical three compartment pharmacokinetics, both in the mouse[16] and humans[17] with hepatic clearance as the dominant mode of excretion. By the intravenous (IV) route, this drug has shown on a weekly schedule major responses between 26% and 44% (depending on the dose) in untreated non–small-cell lung cancer[18] and a 40% major response rate in untreated breast cancer,[19,20] confirming early reports of antitumor activity.[21] Major toxicities at 30 mg/m^2 IV weekly are leukopenia, phlebitis, alopecia, constipation, and rare neuropathy. As expected, previously treated patients have a lower response rate (eg, 16% in small-cell lung cancer).[22] Responses in small numbers of patients have also been noted in lymphoma, esophageal carcinoma, rectal carcinoma, and cervical cancer.[23] This drug has also been administered by infusion over 4 days in a variety of previously treated breast cancer patients with an increasing response rate related to increases in delivered dosage. The investigators[24] used 8 mg IV push followed by a continuous infusion of 8 mg/m^2 daily for 4 days with half of their patients responding at that level. Major toxicities were leukopenia, mucositis, and alopecia.[24]

This drug has been combined with other agents in phase II trials showing a 74% major response rate in untreated breast cancer when combined with doxorubicin,[25] a 63% major response rate in untreated breast cancer when combined with 5-fluorouracil,[26] an 81% major response rate in refractory or relapsed Hodgkin's disease when combined with ifosfamide, methyl-G, and etoposide,[27] a 65% major response rate in untreated non–small-cell lung cancer when combined with cisplatin, 5-fluorouracil, and folinic acid,[28] and responses in non–small-cell lung cancer when combined with cisplatin.[29] In virtually all the trials using IV administration, the major toxicities have been neutropenia, alopecia, and some episodes of phlebitis. As a single agent, the usual dose is 30 mg/m^2; in

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combination with other agents, the dose is usually 15 to 25 mg/m^2 administered on a weekly schedule. Phase III trials to support a new drug application (NDA) in the United States are underway in breast and lung cancer. Trials of this agent in combination with other drugs are at a more advanced stage in France as the drug was originally developed in that country.

Vinorelbine has also been formulated in an oral form to allow chronic dosing with a 45% bioavailability in early studies. Phase II studies of this agent in capsule form at 130 mg per day in a small number (17) of previously untreated (except for adjuvant therapy) breast cancer patients produced no major responses, but the patients actually only received the drug for a total duration of treatment between 1 and 24 days because of toxicity. Nineteen percent of patients in this study refused to continue the study because of major toxicities of leukopenia, anemia, severe nausea and vomiting, alopecia, and acute diarrhea in 71%.[30] Fifty-nine percent of patients on this schedule showed no leukopenia, possibly suggesting idiosyncratic hematologic toxicity. However, the investigators also noted a possible "chemical instability" that may have further complicated the analysis.[30] Further phase I trials of the oral compound have been undertaken in the United States.

In 22 solid tumor patients with 21 having prior treatment, oral vinorelbine on a weekly dosing schedule at approximately 100 mg/m^2 (using 40 mg capsules) showed a bioavailability of 26% with a peak level achieved at 96 minutes after ingestion. A high clearance of the drug was attributed to first pass hepatic metabolism. Major toxicities were granulocytopenia, nausea and vomiting, and diarrhea.[31] A chronic 21-day phase I oral dosing schedule has noted grade 4 neutropenia in 1 patient at 30 mg per day with major toxicites being gastrointestinal. Maximum tolerated dose has not been reached.[32]

Many of these toxicities have been previously observed with oral use of other vinca alkaloids. In the case of one vinca analog, vinzolidine (Eli Lilly, Corp.), clinical trials of the oral formulation were discontinued because of unpredictable hematologic toxicity.

Vinorelbine has also been investigated in an implantable slow-release polymer of D,L lactic and glycolic acids. These implants were evaluated in nine patients with squamous cell carcinoma of the head and neck. Local inflammatory reactions were common but could be controlled with nonsteroidal anti-inflammatory agents. The implants caused local necrosis of the tumor with a release of 45% to 76% of the total drug. At the time of surgery for removal of the tumor, viable tumor was still present.[33]

Vinorelbine is an active drug but the critical studies to show that this agent has any advantage over currently available vinca alkaloids await presentation.

Vintripol

As previously noted, numerous analogs of vinblastine have been synthesized with the majority of those agents showing antitumor activity having modifications confined to the vindoline moiety. In an attempt to change the cellular pharmacology and antitumor spectrum of vinblastine, 21 derivatives of the C23 position of the vindoline ring were prepared with an amide linkage to amino acid carboxylic esters. Vintripol (vintrypol), having a bioisoster of tryptophan (an alpha amino phosphonic derivative), had increased lipophilicity and a broadened antitumor spectrum in murine tumor models compared with vinblastine and vindesine. Long-term survivors were observed in mice bearing P 388 leukemia, and antitumor activity was noted in the murine leukemia L 1210 in vitro model.[34] High antitumor activity could be related to the stereochemistry of the alpha amino phosphonate substitution with the S epimer being active while the R form was relatively inactive. Binding to tubulin was similar for both epimers. However, the R epimer is more slowly expelled from cells, suggesting that retention was important for the antitumor effects.[35] This finding is of significance because, not only are minor substitutions on the vinca alkaloid structure biologically important, but also the configuration of the modification (stereospecificity) may be critical for antitumor effect.

Pharmacokinetic studies in eight patients have shown little interpatient variability, which is in stark contrast with all other vinca alkaloids studied, and a terminal half-life of approximately 20 hours.[36] Phase I trials of this agent in humans as a rapid IV infusion over 5 minutes

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repeated weekly showed rapidly reversible neutropenia and no evidence of neurotoxicity. Dryness of the mouth immediately after injection was also noted. The suggested dose for phase II trials was 30 mg/m^2.[37] Another phase I study on the same schedule noted drug fever, mild nausea and vomiting, and dose-limiting neutropenia and thrombocytopenia.[38] However, this drug also displayed interpatient differences in hematologic toxicity with 36% of courses at the maximum tolerated dose (45 mg/m^2) showing no evidence of leukopenia. Grade 3 or 4 leukopenia toxicities were first noted at doses of 34 mg/m^2 and above.[38]

A phase II study of this agent in non–small-cell lung cancer using a dose of 40 mg/m^2 IV weekly did not show antitumor activity. One half of the study patients had either grade 3 or 4 neutropenia.[39] Another phase II study of this agent failed to document significant antitumor activity in melanoma or colorectal carcinoma.[40] Additional trials are in progress, but the future of this analog is in question unless a schedule with marked antitumor activity can be established.

Vinxaltine (S 12363)

Vinxaltine (Servier, France) shares with vintripol the chemical modification of C23 of the vindoline structure to enhance lipophilicity and cellular retention of the active agent. For vinxaltine, a bioisoster of valine rather than tryptophane is the substitutant at the C23 position. As with vintripol, the addition of the alpha amino phosphonate leads to a stereospecific effect with the S epimer (S 12363) having significant antitumor effects and the R epimer (S 12362) being relatively inactive.[41,42] Vinxaltine is an order of magnitude more cytotoxic than either vincristine or vinblastine and is believed to be the most potent vinca alkaloid described so far.[42] The antitumor activity of this compound could not be explained by its affinity for tubulin, thus suggesting enhanced cellular retention as a mode of its greater cytotoxic effect.[42] Vinxaltine is a better inducer of tubulin spiral at higher doses than is S 12362.[43] However, the difference between these two epimers is mainly caused by the lack of retention of S 12362 in cells in contrast with vinxaltine.[44] This agent was found to strongly inhibit human tumor lines.[45] Prolongation of the duration of exposure of tumor cells to this compound enhanced cytoxicity,[46] suggesting that the maximal antitumor effect may be schedule dependent.

This agent has been studied clinically in three schedules: weekly, biweekly, and 3 consecutive days repeated every 21 days. On a weekly schedule, leukopenia was dose-limiting at 0.40 mg/m^2 with a suggested phase II dose of 0.32 mg/m^2 and a terminal half-life of 12 hours.[47] A similar phase I study of the drug administered weekly for 3 consecutive weeks showed a maximum tolerated dose of 0.50 mg/m^2 with neutropenia dose-limiting. Constipation, mild hepatotoxicity, fatigue, and decreased tendon reflexes were also noted. One patient with melanoma who had failed to respond to Vindesine obtained a partial response.[48] In vitro, this agent is 8 to 370 times more active against melanoma cell lines than is vincristine, vinblastine, or vindesine.[49] A phase I study of every other week dosing showed that the maximum tolerated dose was greater than 0.60 mg/m^2.[50] Peripheral neuropathy has been noted on a daily times 3 dosing schedule.[51] Phase II trials are underway in Europe.

Rhizoxin

This compound is a macrocyclic lactone with a structure more akin to maytansine than the vinca alkaloids, but it is included in this review because it is undergoing evaluation in clinical trials and inhibits microtubular assembly.[52] The majority of preclinical work on this compound has occurred in Europe under the direction of the European Organization for Research and Treatment of Cancer (EORTC). It is known to be an order of magnitude more active than vincristine in cell lines in vitro.[53] This agent originated from the fungus *Rhizopus chinensis,* was found to have a broad preclinical antitumor spectrum, and displayed activity in vincristine-resistant cell lines.[53] In vitro, rhizoxin is a weak competitive inhibitor of vinblastine binding to tubulin and shows non–vinca-like properties.[52] The drug is known to bind to β-tubulin and resistance can be correlated with amino acid changes in tubulin.[54] A derivative, palmitoylrhizoxin (RS-1541) is in preclinical testing.[55]

In vivo studies have shown rhizoxin to be highly protein bound with nonlinear pharmaco-

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kinetics as the dose is increased. The current analytic assay for this compound is not sufficiently sensitive to perform full pharmacokinetic studies in humans.[56] In humans, the maximum tolerated dose was found to be 2.6 mg/m^2 with major toxicities of mucositis, diarrhea, and leukopenia. Minor activity was noted in heavily treated patients with breast cancer. The phase II suggested dose is 2.0 mg/m^2 IV every 21 days.[57] Further studies are in progress in Europe under the EORTC drug development mechanism. In the United States, the drug is currently under development under the NCI clinical trials mechanism with particular emphasis in evaluating this agent in breast cancer.

CONCLUSIONS

Vinorelbine is currently the most studied of these new tubulin-binding agents and because of its demonstrated activity in breast and lung cancer will probably be commercially available within the next few years in Europe and perhaps the United States. In the United States, analogs of anticancer agents have not been approved by the FDA unless they can be shown to be superior to the commercially available parent drug or have a unique attribute (such as less toxicity). Vinorelbine is well tolerated, but the critical trials to show its superiority over the parent compounds are still in progress.

Less is known about the other vinca alkaloids in clinical trials. Schedule of drug administration may be important for both vintripol and vinxaltine in order to show significant antitumor activity in humans. These agents continue to be evaluated in Europe and their ultimate role, if any, remains unclear. Rhizoxin is currently under development in several countries because of its unique structure, preliminary antitumor activity in human breast cancer, and in vitro activity in vinca-resistant cell lines. In the United States, this agent is available through the NCI drug development program. The future place of this agent in treatment of human cancer remains unclear at the present time because of the early stage of development.

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